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THE ACTION OF DOPAMINE ON THE ARTERIAL BLOOD PRESSURE OF THE GUINEA-PIG

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The depressor action of dopamine (β-3 : 4-dihydroxyphenylethylamine) upon the arterial blood pressure of the guinea-pig has been studied. This effect begins without a latent period. It is often enhanced after the intravenous injection of iproniazid (Marsilid). The depressor response is sufficiently sensitive to serve as a method of bioassay of dopamine in microgram quantities. Observations on the depressor action of L-dopa have also been made. This effect is also enhanced by iproniazid; it begins after a latent period. Epinine (β-3 : 4-dihydroxyphenylethylmethylamine) caused a pressor response, followed by a fall of arterial blood pressure. No evidence was obtained in support of the suggestion that the two amines, which are oxidized at similar rates by amine oxidase, cause a fall of blood pressure after their conversion to an aldehyde by the action of amine oxidase.

In addition to noradrenaline and adrenaline, there occurs in mammals a third catechol amine: this is dopamine (hydroxytyramine, β-3 : 4-dihydroxyphenylethylamine) (Goodall, 1951). It is now known that dopamine is the immediate precursor in the formation of noradrenaline in chromaffin tissue and adrenergic nerves.

The biological activity of dopamine has been known for a long time (Barger and Dale, 1910: Gurd, 1937; Holtz, Heise and Lüdtke, 1939). In most preparations, the amine has sympathomimetic activity, but it is less potent than adrenaline or noradrenaline.

A response to dopamine which differs qualitatively from that to the other two naturally occurring catechol amines was described by Holtz and Credner (1942). These authors made a comparative study of the action of dopamine on the arterial blood pressure in different species, and they found that, in the guinea-pig and, to a lesser extent, in the rabbit, dopamine caused a fall in the arterial blood pressure. This finding has been confirmed by Schümann (1956), who used the lowering of the blood pressure in the guinea-pig for the determination of dopamine in extracts of splenic nerves and sympathetic ganglia (see also Dengler, 1957). The fall of the blood pressure after administration of dopamine was ascribed by Holtz and Credner (1942) to the action of the aldehyde produced when dopamine is oxidized by the enzyme amine oxidase. It is known that dopamine is very rapidly oxidized by this enzyme (Blaschko, Richter, and Schlossmann, 1937).

The fact that dopamine has an action different from that of the other two catechol amines is of interest. It is at present not known if dopamine has any regulatory functions in addition to its metabolic rôle as the immediate precursor of noradrenaline.

The experiments to be described were undertaken in order to find out, firstly, if the response of the arterial blood pressure of the guinea-pig to dopamine could serve as the basis for a method of assay and, secondly, whether support for the rôle of amine oxidase in the depressor response to dopamine in the guinea-pig could be obtained.

METHODS

Male guinea-pigs of 400 to 650 g. were anaesthetized with ethyl urethane (2 g./kg. body weight given subcutaneously). A polythene tube was introduced into the right jugular vein and heparin, 10 mg./kg., was administered. The left carotid artery was cannulated and the blood pressure was recorded, using the mercury manometer described by Condon (1951). All substances were administered intravenously and the volume injected was kept constant in each experiment; usually it was 0.3 ml. All doses are given in terms of the base.

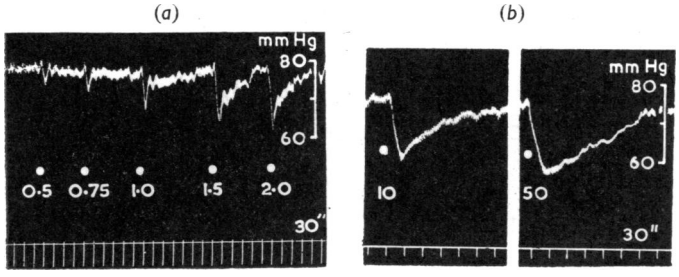

FIG. 1.—Effect of dopamine on the arterial blood pressure of the guinea-pig. (*a*), Guinea-pig, 450 g. urethane anaesthesia. Response of the arterial blood pressure to increasing doses (0·5 μg. to 2·0 μg.) of dopamine, injected intravenously. (*b*), Guinea-pig, 600 g. urethane anaesthesia. Effect of large doses (10 μg. and 50 μg.) of dopamine.

RESULTS

Relation Between Dose and Response.—The response of the arterial blood pressure of the guinea-pig to different doses of dopamine is shown in Fig. 1. In Fig. 1*a*, doses from 0.5 to 2.0 μg. were given ; the depressor response increased with increasing dose. Fig. 1*b* is from another animal in which doses of 10 μg. and 50 μg. were given. In all these experiments the fall of blood pressure was immediate, without any sign of a latent period.

Effect of L-*Dopa and Epinine.*—Experiments were also carried out in which L-dopa was injected. In agreement with observations by Holtz and Credner (1942) dopa caused a fall in the arterial blood pressure, but this began after a brief latent period and was more protracted than with dopamine. The typical response to a small dose of dopa (200 μg.) is shown in Fig. 2.

Fig. 3 shows the typical response to an injection of 10 μg. of epinine (β-3:4-dihydroxyphenylethylmethylamine). The immediate response was a rise of the arterial blood pressure followed by a fall, similar in duration to that caused by dopamine.

Effect of Iproniazid.—In a number of experiments iproniazid was given in order to inhibit the action of amine oxidase on dopamine. Dopamine

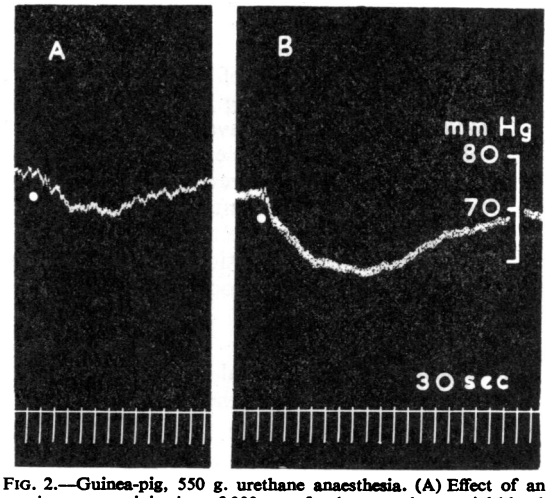

FIG. 2.—Guinea-pig, 550 g. urethane anaesthesia. (A) Effect of an intravenous injection of 200 μg. of L-dopa on the arterial blood pressure; (B) effect of the same dose of dopa, 90 min. after iproniazid, 40 mg./kg. intravenously.

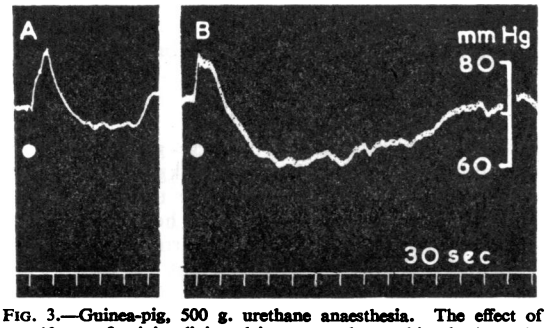

FIG. 3.—Guinea-pig, 500 g. urethane anaesthesia. The effect of 10 μg. of epinine (injected intravenously at white dots) on the arterial blood pressure (A), before and (B), 90 min. after an intravenous injection of 40 mg./kg. iproniazid.

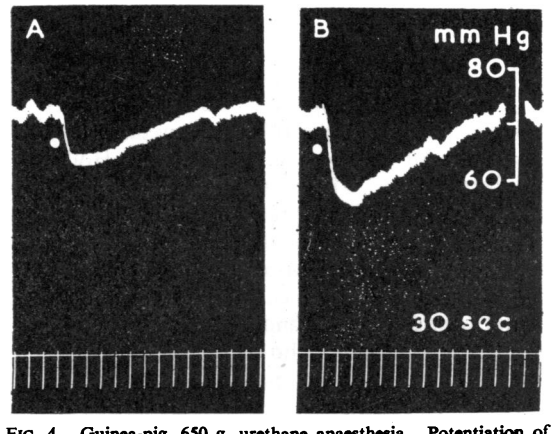

FIG. 4.—Guinea-pig, 650 g. urethane anaesthesia. Potentiation of the depressor effect of dopamine by iproniazid. (A), Response of the arterial blood pressure to 5 μg. of dopamine before and (B), 90 min. after an intravenous injection of 40 mg./kg. of iproniazid.

was injected before, and 90 min. after, an intravenous injection of 40 mg./kg. of iproniazid.

In none of these experiments was there a diminished depressor response to dopamine after iproniazid ; in most the response to dopamine after iproniazid was enhanced and sometimes prolonged. Fig. 4 shows the response to 5 μg. of dopamine before and after iproniazid.

Experiments on the effect of iproniazid on the depressor action of dopa were also carried out. Here, too, an enhancement of the depressor response usually occurred. This can be seen in Fig. 2, where 0.3 mg. of dopa was injected.

Oxidation Products of Dopamine and Epinine.—In order to obtain information on the action of the products of oxidation of the two amines by amine oxidase, a manometric experiment was carried out in which an enzyme preparation was incubated with either epinine or dopamine ; the incubation was terminated just after about 0.5 molecule of oxygen/molecule of substrate had been taken up. For this experiment an acetone-dried preparation of guinea-pig liver was used. Each manometer flask contained 50 mg. of powder, thoroughly washed with 0.067 M-sodium phosphate buffer of *p*H 7.4. At the zero moment, 0.2 ml. of an 0.05 M solution of amine hydrochloride was tipped in from the side arm of a conical manometer flask. The total volume of fluid in each flask was 2.0 ml.; the gas phase was O_2 and the temperature was 37.5°.

The initial rates of oxygen uptake with dopamine and epinine were similar. Two vessels, one with dopamine, the other with epinine, were removed after 27 min., when the oxygen uptake was 127 and 138 μl. respectively. The samples were quickly centrifuged at 0°, and fractions, suitably diluted, were injected intravenously. Another pair of samples was incubated for 39 min., when the uptake of oxygen was 141 and 155 μl. respectively.

The samples which had been incubated with dopamine caused a very slight fall in blood pressure ; the samples incubated with epinine caused a rise, followed by a fall, similar to that produced by the injection of an aqueous solution of epinine. However, the size of the responses to the incubated samples was much less than that to the injection of the corresponding amount of amine not incubated with a preparation containing amine oxidase. In other words, there was no indication that the fall of arterial blood pressure was greater after incubation.

Action of Dopamine on the Heart Rate.—The heart rate before and after an injection of dopamine was recorded by means of an electrocardiograph (Lead II). There was no change in the rate after intravenous injection of 2 μg. of dopamine ; after 100 μg. the rate fell from 280 beats/min. to 260.

Discussion

The experiments described in this paper confirm earlier observations, in which it was shown that dopamine lowers the arterial blood pressure in the guinea-pig. The depressor effect was constant and could usually be elicited by relatively small amounts of the amine. This shows that this effect can serve as the basis of a quantitative determination of dopamine.

The cause of the depressor effect is not known. Holtz and Credner (1942) suggested that it was due not to the action of dopamine itself, but to that of the aldehyde formed from it by enzyme action. It is difficult to reconcile this interpretation with some of the observations reported. Firstly, the response was prompt, without any visible latent period. Secondly, the response to epinine differed from that to dopamine, although both amines are oxidized by guinea-pig amine oxidase at a similar rate (Blaschko *et al.*, 1937 ; Beyer, 1943 ; Randall, 1946). This was confirmed in the present experiments. The two amines should give rise to the same aldehyde as the primary product of oxidation. Thirdly, iproniazid, an inhibitor of amine oxidase, did not abolish or diminish the depressor reaction ; on the contrary, in most experiments, the fall of blood pressure was enhanced and prolonged after iproniazid. It has recently been questioned whether iproniazid is as effective an inhibitor of amine oxidase *in vivo* as it is *in vitro* (Udenfriend, Weissbach, and Bogdanski, 1957). That the drug does inhibit the breakdown of dopamine *in vivo* is supported by observations of Balzer and Holtz (1956), who have shown that in guinea-pigs treated with iproniazid the amounts of dopamine excreted in the urine after administration of dopa were almost doubled. In the present experiments, iproniazid enhanced the depressor response to dopa whenever the response to dopamine was potentiated.

The depressor action of dopamine was not due to an effect on the heart rate because doses which caused a marked fall of blood pressure were without significant action upon the heart rate.

I wish to express my thanks to Professor J. H. Burn, F.R.S., for the opportunity of working in his department and to Dr. H. Blaschko for his help in the manometric experiment and for his constant advice and encouragement. The work was done during the tenure of a British Council Scholarship.

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